

REMARKS / ARGUMENTS

Rejections Withdrawn

Applicants acknowledge the Examiner's withdrawal of both rejections of pending claims 1-16 under 35 USC 103(a).

New Grounds of Rejection

35 USC 112, second paragraph

Claims 2, 5, 9 and 14 stand rejected as being indefinite for the recitation of "zwitterionic detergent." Applicants traverse the rejection.

In the Office Action dated December 14, 2004, the Examiner rejected claims 1-16 because the recitation of trademarks allegedly rendered the claims indefinite. To overcome the rejection, Applicants amended the claims by replacing the trademarks with their generic terminology to identify the particular materials. Applicants also amended the specification to be consistent with the amended claims. See Amendment filed May 19, 2005. For instance, the term "Zwittergent™ compound" was replaced with "zwitterionic detergent." (See May 19, 2005 Amendment, page 3) This term was defined in the new paragraph inserted at page 13, before line 30, of the specification: "The term 'zwitterionic detergent' refers to a detergent that is electrically neutral overall, but has a positively charged moiety and a negatively charged moiety and is commonly used to solubilize hydrophobic proteins." (See May 19, 2005 Amendment, page 3.) The Examiner withdrew her rejection in the Office Action dated September 9, 2005.

Since Applicants have already overcome this rejection, Applicants respectfully request that it again be withdrawn.

35 USC 103(a)

Claims 1-16 stand rejected as allegedly being obvious over a new combination of references: Green et al. (U.S. Patent No. 5,780,601) (previously cited and discussed) in view of Nicholson (U.S. Patent No. 5,681,936). The Examiner contends that one skilled in the art would have been motivated to combine the tangential flow filtration (TFF) taught by Nicholson with the differential detergent extraction taught by Green et al. to extract bacterial proteins "because Nicholson teaches that using TFF has the benefit of high yields and entirely homodimeric." Applicants traverse the rejection.

The Examiner ignores the main points of the Nicholson '936 patent, which clearly states that *after removing cells* from a cell culture expressing human interleukin-5, IL-5 is purified by first adjusting *the culture supernatant* to the calculated pI value of mature IL-5 (col. 6, lines 41-43). That is, the Nicholson '936 patent is directed to methodologies that specifically allow the mammalian cells to remain intact and not be lysed, whereas the claimed invention specifically deals with the critical combination of lysed bacterial cells and tangential flow filtration. As stated previously (see July 6, 2006 Amendment, page 3), TFF is typically used in processes to avoid the lysis of cells, as the lysed content tends to clog filters. Thus, one skilled in the art would be motivated to **avoid** using TFF when dealing with a preparation of lysed bacterial cells. The Nicholson '936 patent does not make any special points about TFF and its use in the process for purification of IL-5. Rather, the Nicholson '936 patent states that "conditioning resulting in a conditioned cell culture is intended to include, but not [be] limited to . . . removal of low molecular weight components (e.g. constituents of the cell culture medium (inorganic salts, vitamins, amino acids) as well as metabolites excreted by the cells during their maintenance in culture) by ultrafiltration or diafiltration (or dialyzing) . . .", thus providing any commonly known method of separating low molecular weight components from those of higher molecular weight as acceptable. No direction to the benefits of TFF is given anywhere in the Nicholson '936 patent, nor is it in any way taught as being superior to any other method for the use described. Moreover, there is no teaching or suggestion that TFF be combined with the differential detergent extraction of Green et al. to obtain the claimed invention.

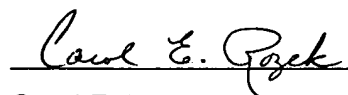
In the presently claimed invention, the inventors detail the utilization of TFF in a process in which the first step is *lysis* of bacterial cells, combined with differential detergent extraction of membrane proteins. This initial lysis will release nucleic acids and contaminating proteins, situations that clearly do not apply to the purification described by Nicholson. Since one of the main benefits of TFF known at the time was its low sheer forces and ability to keep mammalian cells intact, it is unlikely that one skilled in the art would be taught by Nicholson to try TFF for process purification of the bacterial membrane proteins. Nicholson only teaches a method for purification of soluble IL-5 in the supernatant in which one of the initial steps **could be TFF**. Furthermore, one skilled in the art would know that differential detergent extraction is performed at or above the critical micelle concentration (CMC) of the detergent, assuring

that the detergent and extracted membrane proteins will mostly be in micelles. The unobviousness of the claimed invention is the ability to use TFF with all of these factors that one would have thought should mitigate its use. The Nicholson '936 patent makes no mention of the use of detergent, and presents the use of TFF as a method suited to situations where one has a soluble protein **after removal** of the producing cells. The Nicholson '936 patent makes no references to any of the factors that the inventors overcame in the successful use of TFF in the claimed invention, including how to ascertain that one could move detergent micelles through a tangential flow filter without clogging, how to choose filters for such a use, how to change detergents, what criteria are used to judge such parameters, etc. Nicholson at best serves as a mention of TFF as a possible methodology for separating low molecular weight components from high molecular weight ones, but teaches away from its use in the instance of the situation faced by the inventors of the present invention.

Since the combination of the Green and Nicholson patents does not render the claimed invention obvious, Applicants submit that the rejection is improper and should be withdrawn.

In view of the above remarks, Applicants submit that the present application is in condition for allowance, and a Notice to that effect is requested.

Respectfully submitted,



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